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Review

Outcome-centered antiepileptic therapy: Rate, rhythm and relief. Implementing AAN Epilepsy Quality Measures in clinical practice

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ABSTRACT

Clinicians who manage patients with epilepsy are expected to assess the relevance of clinical trial results to their practice, integrate new treatments into the care algorithm, and implement epilepsy quality measures, with the overall goal of improving patient outcomes. A disease-based clinical framework that helps with choice and combinations of interventions facilitates provision of efficient, cost-effective, and high-quality care. This article addresses the current conceptual framework that informs clinical evaluation of epilepsy, explores gaps between development of treatment options, quality measures and clinical goals, and proposes an outcome-centered approach that bridges these gaps with the aim of improving patient and population-level clinical outcomes in epilepsy.

1. Introduction

Despite modern advances in antiepileptic therapy, the burden of epilepsy continues to be a major clinical challenge. The burden of seizures is compounded by associated neurological comorbidities and adverse effects of treatment. Moreover, epilepsy is the second highest among neurological disorders in years of potential life lost (YPLL) [1]. Various groups involved in clinical care and research and development (e.g., clinicians, regulators, industry and health policy personnel, payers) address these challenges within separate frameworks which are appropriate to their respective enterprise. This article addresses the current conceptual framework that informs clinical evaluation of epilepsy, explores gaps between various frameworks, and proposes an outcome-centered clinical approach that bridges these gaps with the aim of improving patient and population-level clinical outcomes in epilepsy.

2. Clinical evaluation

Clinical evaluation in patients with epilepsy includes assessment of frequency, severity and duration of seizures, comorbidities and side effects of treatment, and adherence to treatment regimens. Epilepsy quality measures have been recently updated to standardize clinical assessments [2]. These measures and assessments reflect biological principles (Fig. 1) and help clinicians to formulate and revise treatment plans. Results are typically assessed by seizure freedom rates and quality-of-life measures. When treatment goals cannot be achieved with standard treatments, patients may be enrolled in clinical trials.

3. Gaps between trials and clinical goals

The same biological principles used to formulate treatment plans inform clinical development of antiepileptic therapies, and results of controlled trials should, in theory, align with clinical effectiveness. Gaps are created when there is incomplete alignment between different frameworks for clinical development and practice (Table 1). Development of treatment options for epilepsy could potentially target any of the disease domains — seizure frequency, severity, or duration or quality-of-life effects — that influence clinical outcomes. However, clinical trials are designed to assess efficacy of intervention on a prespecified single primary endpoint. Due to the well-known and reliable effect of antiepileptic drugs on seizure frequency, all clinical trials for antiepileptic drugs (AEDs) and devices evaluate effect on intervention on the same primary endpoint — seizure frequency.

Since clinical trials of adjunctive AED therapy enroll patients who have persistent seizures despite adequate doses of two or more standard treatments, these patients typically meet the ILAE definition of drug-resistant epilepsy [3]. The possibility of seizure freedom with another drug in a patient with drug-resistant epilepsy is considerably lower than that expected with *de novo* use of AEDs [4,5]. Hence, clinical trials are typically designed and powered to assess a fractional reduction in seizure frequency rather than seizure freedom (endpoint gap between goals in practice and trials). Based on regulatory guidelines, a comparator is required to demonstrate benefit, in superiority (US) or

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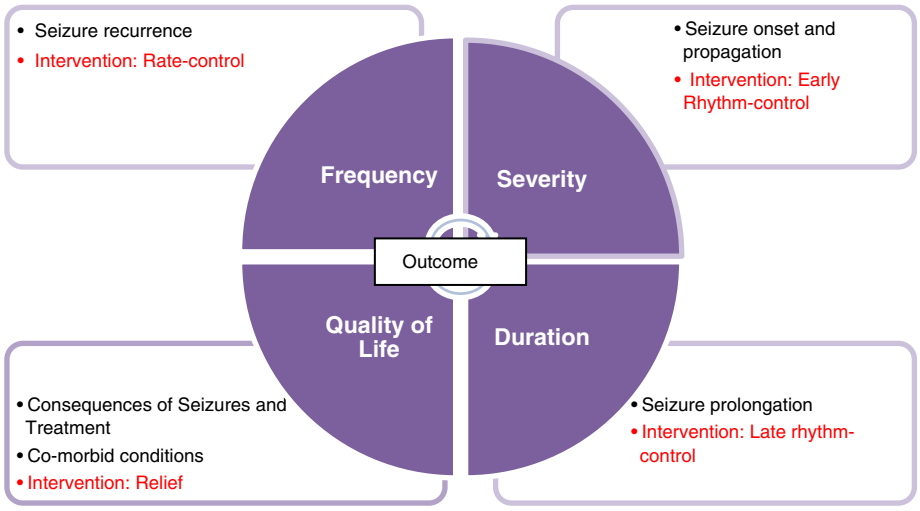

Fig. 1. Disease domains, underlying biological principles, and interventions.

noninferiority (EU) trials. Efficacy of antiepileptic drugs and devices in clinical trials is established as superiority to placebo or noninferiority to standard AEDs (design gap). Unlike clinical practice where sustained seizure freedom is measured in years, controlled trials last for a matter of months (duration-of-assessment gap). Moreover, unlike a practice cohort where clinical effectiveness is desired for all patients started on an intervention, efficacy in controlled trials is assessed on a narrow disease spectrum (defined by inclusion and exclusion criteria), and long-term efficacy is often reported on completer cohorts, rather than enrolled population. Since retention rates in clinical trials typically drop over time, whereas clinicians manage all patients over time, this creates another gap (cohort gap) between trial and practice.

Successful trials using the current approach are the basis of regulatory approval of all new therapies. While randomized trials provide high-quality evidence, clinical and trial frameworks are not aligned due to these gaps. Hence, it should not be surprising that there is no appreciable change in seizure freedom rates despite availability of multiple new drugs and devices for clinical use [5].

4. Bridging gaps between trials and clinical practice

From a clinical practice perspective, the benefit of novel interventions may be enhanced by demonstrating superiority of a novel intervention to standard-of-care on a prespecified, clinically relevant, primary endpoint (e.g., seizure freedom for a seizure frequency endpoint). The primary endpoint can target disease domains beyond seizure frequency — severity, duration, and quality of life — in pivotal trials, in order to align interventions with clinical goals. Thus, all four clinical domains present potential opportunities for improvements in future development of treatment options. Impact on health-economic and health-care utilization over longer periods can be incorporated into "real-world" trials designed to demonstrate both clinical- and cost-effectiveness of novel interventions over standard-of-care.

Table 1
Gaps between trials and practice.

Type of gap	Trials	Practice
Endpoint gap	Seizure reduction	Seizure remission
Design gap	Noninferiority to SOC[a]	Superiority to SOC[a]
Duration of assessment gap	Weeks/months	Years
Patient cohort gap	Limited spectrum, completers	Full spectrum, enrolled
Domain gap	One clinical domain	All clinical domains

[a] Standard of care.

From a clinical trials perspective, the initial challenge is formulating a generally accepted clinical standard-of-care based on disease characteristics and clinical domains. The next set of challenges includes developing trial models and development plans that target various domains, followed by outcome-oriented endpoints (see below). Recent advances in genetics, epilepsy network analysis, and application of predictive analytics to large datasets provide the means to test and develop new approaches for subpopulations and disease subsets. The opportunity is the aim and promise of superior outcomes over current standard-of-care.

5. Optimizing antiepileptic therapy

We need a treatment approach that defines, rather than being limited or defined by, clinical trial endpoints. We need to consider approaches that combine therapies to further improve outcomes beyond reduction in seizure frequency.

In patients with persistent seizures, quantity of seizures is an important, but not the sole, factor that influences quality of life. Seizure worry and depression, side effects of drugs, comorbidities, and lack of adherence are nonfrequency related factors that impact quality-of-life outcomes [6–8]. A treatment approach that focuses on optimizing outcomes should target all four disease domains that are routinely assessed in clinical practice. In neurology, migraine offers an example of combining prophylactic, symptomatic, and lifestyle interventions to reduce the burden of disease. A similar disease-based clinical framework approach may be considered in epilepsy.

6. Outcome-centered antiepileptic therapy: a disease-based clinical framework

In other areas of medicine (notably cardiology), multimodal approaches that offer unique and complementary benefits are routinely combined in care algorithms. While neural networks are considerably more complex than cardiac conduction pathways, there are similarities in clinical expression that could inform similar treatment approaches (Table 2). Both epileptic disorders and cardiac rhythm disorders share common biological factors of genetic predisposition, abnormal organ substrate, and systemic/environmental triggers that lead to an enduring predisposition to "arrhythmias". Interictal electrophysiological abnormalities may be present on both the EEG and ECG, with or without activation procedures, and paroxysmal events in both systems have well-defined onset, propagation, and recurrence patterns. Comorbidities contribute to poorer outcomes in both epilepsy and cardiac disease.

Table 2
Treatment approaches — biological basis in cardiology and epilepsy.

Approach	Biological basis	Cardiac arrhythmia	Antiepileptic therapy
Rate-control therapy	Manage rate	Control ventricular rate	Control seizure rate (frequency)
Rhythm-control therapy	Detect and prevent propagation and/or prolongation of abnormal activity	Restore sinus rhythm after onset of arrhythmia	Restore EEG to non-ictal patterns after onset of seizure
Relief therapy	Reduce disease and treatment burden (comorbidities, adverse events)	Manage systemic disease, stressors, improve quality of life	Manage CNS comorbidities and stressors, improve quality of life

Thus, investigational and treatment approaches that have been successfully used to improve outcomes in cardiology may be explored to improve outcomes in epilepsy.

Outcome-centered antiepileptic therapy integrates various complementary approaches — rate, rhythm and relief — to link treatments to established clinical goals and optimize clinical outcomes (Table 3).

6.1. Rate-control therapy

The ultimate clinical goal of reducing the rate or frequency of seizures (rate-control therapy) is sustained seizure freedom, *without unacceptable side effects*. Seizure freedom is achieved in approximately two-thirds of patients with epilepsy with antiepileptic drug therapy [5]. Epilepsy surgery offers a median of 62.4% seizure freedom rate in surgically eligible patients with drug-resistant focal epilepsy [9] and is the preferred rate-control therapy for these patients. For patients with drug-resistant epilepsy who are not seizure-free (both postsurgical and nonsurgical), diet- and device-based therapies (e.g., VNS, RNS) offer other options for rate-control therapy. The combination of *multimodal* rate-control therapies is one example of optimizing treatment outcomes and is underutilized in clinical practice despite offering convincing clinical benefit [10,11].

Although necessary, rate-control therapy is insufficient when seizure freedom without unacceptable side effects is clinically infeasible. In these patients, a substantial portion of the morbidity and mortality risks is due to the clinical consequences of the other disease domains and requires other therapies targeted toward these domains. Since rate-control therapies are emphasized in clinical practice, further details are omitted here to focus on other therapeutic approaches.

6.2. Rhythm-control therapy

Unlike rate-control therapies which aim to reduce the frequency of clinical events, rhythm-control approaches are activated at or after onset of an "arrhythmic" event to reduce severity, duration, and adverse clinical consequences (e.g., implanted cardioverters-defibrillators). A considerable amount of epilepsy-related morbidity (falls, fractures, burns, accidents, etc) is due to the severity of seizures. The clinical goal of rhythm-control therapy in epilepsy is to limit the propagation of a seizure across the epileptic network and reduce the associated clinical consequences. These therapies may be classified as early or late, depending on the interval between onset of a seizure and delivery of therapy.

Early rhythm-control therapies are interventions at or following onset of a seizure. While early rhythm-control therapy in arrhythmias is standard-of-care in cardiology, we do not have controlled clinical trials for similar therapies in epilepsy. Hence, clinical use of available rhythm-control approaches is based on observational clinical data. In epilepsy, these include device-based open-loop and closed-loop options. With the use of open-loop magnet mode of VNS therapy, 45% of patients report clinical benefit on seizure severity, duration, or recovery, with 28% reporting cessation of seizures [12]. These effect sizes of rhythm-control therapy on seizure duration and severity are comparable to those of drugs and device-based rate-control therapies on seizure frequency. Closed-loop options, such as responsive neurostimulation(RNS) and the AspireSR VNS device, automate rhythm-control therapy. Investigation and utilization of early rhythm-control approaches to reduce seizure severity and duration are a clinically relevant opportunity for future antiepileptic therapy development.

Late rhythm-control therapy is a "fail-safe" to manage seizures that continue despite early rhythm-control approaches. The use of benzodiazepines, as rescue therapy for repetitive seizures and for acute intervention of prolonged seizures, represents the most commonly used late rhythm-control therapy. This reactive approach is intended to limit morbidity associated with repetitive or prolonged seizures. Treatment of status epilepticus is, in essence, an urgent late rhythm-control strategy (details of treatment of status epilepticus are beyond the scope of this article).

Successful rhythm-control approaches would be expected to hinder the progression of seizures to generalized convulsive seizures or status epilepticus. The use of appropriate rhythm-control strategies can contribute to better outcomes by alleviating severity and duration of clinical events as well as patient/caregiver concerns (i.e., seizure worry) regarding these domains.

6.3. Relief therapy

Network effects associated with epilepsy, comorbidities, and side effects of antiepileptic therapies are a significant contributor to poor quality of life, especially in patients with drug-resistant epilepsy. In these patients, optimizing outcomes by relieving the burden of these factors (hence, "relief" therapy) is another clinical challenge and opportunity. Yet, this opportunity is often overlooked, especially when a treatment approach is predominantly focused on rate-control therapies.

Table 3
Types and goals of interventions in epilepsy.

Type	Goal	Examples of intervention	2014 Epilepsy Update Quality Measurement Set
Rate-control	Reduce seizure frequency Time-basis: long-term	Antiepileptic drugs Surgery Devices Diets	1a (seizure frequency), 2 (disease features), 4 (seizure safety), 7 (referral)
Rhythm-control	Reduce severity and duration of seizures Time-basis: acute	Open-loop device systems Closed-loop device systems Drugs (e.g., benzodiazepines)	1b (seizure intervention), 4 (seizure safety)
Relief	Reduce burden of disease on quality of life Time-basis: ongoing	Treatment side effects management Lifestyle interventions Treatment of comorbidities	3 (side effect management), 5 (psychiatric comorbidities), 6 (counseling for women with epilepsy)

Several opportunities for relief therapy, using multimodal approaches, can either avoid or mitigate the additional burden associated with factors that drive network effects. These are summarized as "TLC" below, borrowing a common clinical care acronym (note — interventions may be similar to those noted earlier; the domain of interest determines the goal of treatment and impact on outcome). Other aspects of care that reduce the nonseizure-related burden can also be considered as relief therapies and, while clinically relevant, are beyond the scope of this article.

6.3.1. T — treatment-associated effects

6.3.1.1. Nonadherence. Nonadherence with AEDs is associated with an over threefold increase in risk of mortality compared to adherence, as well as a higher risk of morbidity and health-care utilization [8]. Combining an active (opt-in) modality such as drugs or diets with an automatic (opt-out) device-modality reduces the risk of treatment nonadherence and epilepsy-related clinical events as well as health-care utilization [13].

6.3.1.2. Side effects. Adverse effects of antiepileptic drugs are associated with poor quality of life in patients with epilepsy [7], and CNS side effects on balance and sedation are nearly universal to all AEDs. Systemic effects of AEDs also need to be evaluated and managed, including systemic and organ toxicity and drug–drug interactions. It is standard-of-care in oncology to combine multimodal approaches to improve treatment response and limit toxicity. Similarly, multimodal approaches in epilepsy, including early surgical referral and drug–device–diet combinations (polytherapy) to reduce CNS side effects and/or treat comorbidities, would considerably reduce the treatment burden associated with multiple drugs (polypharmacy).

6.3.2. L — lifestyle interventions

Sleep disturbances contribute to destabilization of seizure control, and management of sleep disorders offers opportunities for relief therapy, with effect sizes comparable to those of standard antiepileptic therapies [14]. Stress reduction and environmental modifications (especially in reflex epilepsies) provide other opportunities for lifestyle interventions. Excessive alcohol and caffeine consumption and drug abuse may also contribute to destabilizing seizure control and offer potential intervention opportunities. Attention to exercise, diet, and social support are among the generally helpful lifestyle interventions.

6.3.3. C — comorbidities

The prevalence and impact of comorbidities (e.g., migraine, depression, anxiety) are other contributors to poor quality of life in epilepsy and offer opportunities to provide additional relief beyond management of seizures. Network effects that influence cognitive and behavioral domains can also be addressed through specific interventions. Antiepileptic drugs and devices, which are indicated for management of some of these comorbidities, allow judicious choices of therapy to reduce the burden of both disease and interventions [15].

7. Outcome-centered approach: combining rate, rhythm and relief therapies

When evaluating a patient with epilepsy, the points to consider in an outcome-centered approach are the following:

a) Have all disease domains — frequency, severity, duration of seizures, and quality-of-life effects — been evaluated for impact on outcome?
b) Which combination of the three approaches — rate, rhythm, and relief — is most appropriate to achieve the desired outcome?

Since the clinical goal is to improve outcomes at all stages of illness, the proposed outcome-centered approach will lead to different choices of therapy in individual patients. Of note, this approach is well-aligned with bedside clinical assessments and quality-of-life indicators and provides a means of implementing epilepsy quality measures. Applying it consistently in clinical practice will uncover opportunities to improve outcomes at both patient and population levels. Using it as a guide for development of future antiepileptic therapies will lead to novel study designs, with endpoints that represent a confluence of clinical, regulatory, and health economic goals.

Outcome-centered treatment may be viewed as a form of personalized medicine that integrates clinical knowledge, treatment goals, and patient preferences. Colleagues in other specialties, notably cardiology and oncology, use outcome-centered measures, such as quality-of-life measures, disease-free survival and hospitalization, and mortality rates to demonstrate superiority to standard-of-care. By developing and adopting novel outcome-centered interventions and combination therapies, they have served their patients and profession well and improved population-level outcomes at a pace that far surpasses our current approach.

As quality-of-care assessments transition from patient-level to population-level metrics, it is important to identify gaps between conceptual frameworks used for developing treatments, providing point-of-service care, and public health goals. Failure to recognize and bridge these gaps often leads to overutilization of resources without commensurate improvements in quality or outcomes. The outcome-centered approach outlined in this article is grounded in clinical care principles. It allows clinicians, industry and health policy personnel to identify barriers and build bridges to better solutions — and in turn, a better tomorrow for our patients, their caregivers, and society.

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Conflict of interest statement

Dr D'Cruz is an employee of Cyberonics (Chief Medical Officer). Previous employers include UCB Pharma (Medical Director), and University of North Carolina-Chapel Hill (Professor, Neurology and Pediatrics).

References

[1] Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55(10):1479–85.
[2] Fountain NB, Van Ness PC, Bennett A, Absher A, Patel AD, Sheth KN, et al. Quality improvement in neurology: Epilepsy Update Quality Measurement Set. Neurology 2015;84(14):1483–7.
[3] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–77.
[4] Kwan P, Brodie M. Early identification of refractory epilepsy. N Engl J Med 2000; 342(5):314–9.
[5] Brodie M, Barry SJE, Bamagous JA. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548–54.
[6] Loring DW, Meador KJ, Lee GP. Determinants of quality of life in epilepsy. Epilepsy Behav 2004;5(6):976–80.
[7] Perucca P, Carter J, Vahle V, Gilliam FG. Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy. Neurology 2009;72(14): 1223–9.
[8] Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology 2008;71(20):1572–8.
[9] Jobst B, Cascino G. Resective epilepsy surgery for drug-resistant focal epilepsy — a review. JAMA 2015;313(3):285–93.
[10] Labiner DM, Cascino GD. Are neurologists really data driven in selecting epilepsy treatment? Neurology 2012;78(16):1194–5.
[11] Jehi L, Mathern GW. Who's responsible to refer for epilepsy surgery? We all are! Neurology 2015;84(2):112–3.
[12] Fisher RS, Eggleston KS, Wright CW. Vagus nerve stimulation magnet activation for seizures: a critical review. Acta Neurol Scand 2015;131(1):1–8.
[13] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011;22(2):370–5.
[14] Vaughn BV, D'Cruz OF. Sleep and epilepsy. Semin Neurol 2004;24(3):301–13.
[15] Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004;6(2):57–75.